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September 15, 1997

Date

Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Bell, et al.

Serial No.: 08/455,683

Filed: May 31, 1995

For: OPIOID RECEPTORS: COMPOSITIONS
AND METHODS

Group Art Unit: 1812

Examiner: S. Teng

Atty. Dkt. No.: ARCD:177/WIM

SUBMISSION OF DECLARATION OF TERRY REISINE, PH.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully submit a Declaration of Terry Reisine, Ph.D., for filing in this case.

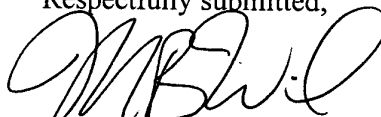
Terry Reisine is one of the named inventors of this application. Dr. Reisine is on the faculty at the University of Pennsylvania. As set forth in his Declaration, attached hereto as Exhibit A, Dr. Reisine has been accused of academic dishonesty by the University of Pennsylvania. Proceedings relating to this allegations are continuing. The Declaration of Terry Reisine sets forth the nature of the allegations against Dr. Reisine.

Applicants' representative and Applicants are submitting the Declaration of Terry Reisine in order to comply with the duty of candor owed to the Patent and Trademark Office in this matter. While it is believed that the Declaration is sufficient to lay these matters to rest, the Examiner, or any other relevant person at the Patent and Trademark Office, is invited to contact Applicants' representative in regard to any additional information which might be helpful in regard to these matters.

Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Arnold, White & Durkee Deposit Account No. 01-2508/ARCD:177/WIM.

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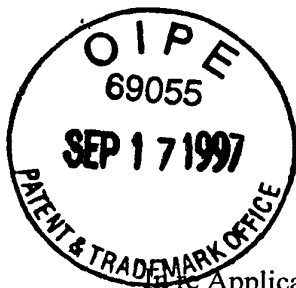
Respectfully submitted,



Mark B. Wilson
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P.O. Box 4433
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Date: September 15, 1997



PATENT

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Bell et al.

Serial No.: 08/455,683

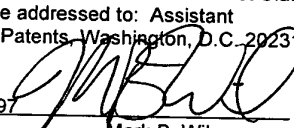
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Date	Mark B. Wilson

DECLARATION OF TERRY REISINE, PH.D.

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I, Terry Reisine, declare as follows:

1. I am one of the named inventors on the above-referenced application.
2. I am submitting this Declaration to comply with the duty of candor owed the Patent and Trademark Office in regard to the above-referenced application.

3. I have been accused of scientific misconduct at the University of Pennsylvania. The accusations are that I fabricated cyclic AMP ("cAMP") data contained in two papers: Kong *et al.*, *J. Biol. Chem.*, 268:23055-23058, 1993 ("Kong") and Raynor *et al.*, *J. Pharmacol. Expt. Therap.*, 270(3):1381-1386, 1994 ("Raynor"). Copies of the Kong and Raynor papers that have been called into question are attached as Exhibits A and B, respectively.
4. I have vigorously disputed these charges of scientific misconduct. These matters have not been resolved, and I am using every reasonable means to clear myself of these allegations. Nonetheless, I recognize the duty to put before the Patent and Trademark Office relevant information relating to these allegations.
5. The presently pending allegations made with regard to the Kong and Raynor papers are that the sample size on various Figures and Tables is misreported.
6. With regard to the Kong paper, charges have been made against me that the sample sizes reported in Figure 2 and Table 1 of this paper have been inflated. The allegation is that I typed the sample size in the paper and therefore committed misconduct by misstating the sample size.
7. With regard to the Raynor paper, charges have been made against me that cAMP experiments I performed were fabricated, and that data in two cAMP figures (Figures 3 and 4) and their legends were falsified.
8. There has been no allegation that the scientific conclusions of either the Kong or Raynor papers are incorrect. The conclusions in the Kong and Raynor papers have not been called into question.
9. There have also been accusations involving two manuscripts which were submitted for publication but were never published, with Livingston as the first author ("initial Livingston manuscript" and "revised Livingston manuscript").

10. The present patent application contains material that is in dispute from both the Kong and Raynor papers, and the Livingston manuscripts. However, the disputed subject matter does not challenge the conclusions of the papers, and is not needed to support the conclusions found in the specification.

11. Paragraphs 12-15 below discuss information from and references to the Kong paper found in the specification; paragraphs 16-21 discuss information from and references to the Raynor paper found in the specification; paragraphs 22-26 discuss information from and references to the Livingston manuscripts; paragraph 27 discusses a reference to an additional publication by Kong *et al.* found in the specification; and paragraphs 28-29 discuss information from a study that was not published that is found in the specification in Example X.

The Kong Paper

12. The Kong paper that has been called into question is Kong *et al.*, *J. Biol. Chem.*, 268:23055-23058, 1993. This paper is referenced on page 189 of the specification. There is another Kong *et al.*, 1993 reference on page 189 of the specification, Kong *et al.*, 1993 (*Mol. Pharmacol.* 44:380), which has not been called into question.

13. At page 82, line 34 through page 86, line 6, and at page 153, lines 24 through 32 of the specification, there is discussion of mammalian delta opioid receptors having an aspartate at residue 95 mutated to an asparagine (D95N). Within this section, at page 153, line 28 of the specification, the Kong paper is referred to. This information is reported in the Kong paper, but is not in dispute. No data is included in the specification on the D95N mutation. Additionally, claim 37 as filed with the original application makes a reference to a mutant opioid receptor polypeptide having an asparagine at residue 95 instead of aspartate.

14. The conclusions of the Kong paper are not in dispute. The data in the Figures and in the Table of the Kong paper are not in dispute. The only information in the Kong paper which is in dispute are the sample sizes described in the legends of Table 1 and Figure 2 of the paper. The data and legends in Figures 1, 3 and 4 of the Kong paper are not in dispute, and support the scientific conclusions of the paper. The conclusions drawn in the specification have not been called into question.

15. The results of the Kong paper have been reproduced in my laboratory, and are presented in a manuscript by Bot *et al.* that has been accepted for publication in the *Journal of Pharmacology and Experimental Therapeutics*, pending minor modifications ("Bot, accepted"). A copy of the accepted Bot manuscript, and a letter from the Editor of the *Journal of Pharmacology and Experimental Therapeutics*, which describes the publication status, is attached as Exhibit C.

The Raynor Paper

16. The Raynor paper that has been called into question is Raynor *et al.*, *J. Pharmacol. Expt. Therap.*, 270(3):1381-1386, 1994.

17. At page 105, line 35 through page 106, line 3 of the specification of the above-referenced application there is a statement:

"Studies in rodents have also suggested that kappa receptors can be modulated by chronic opioid treatment. As expected, the cloned kappa receptors expressed in COS cells are desensitized following agonist pretreatment."

This is a conclusion based on experiments which were reported in the Raynor *et al.* paper. Charges have been made against me that the cAMP experiments I performed for the Raynor *et al.*

paper were fabricated, and that data in two cAMP figures (Figures 3 and 4) and their legends was falsified.

18. At page 192, there is a reference to Raynor *et al.* 1994, *J. Pharmacol. Expt. Therap.* (in press). This paper was published, and is the Raynor paper that has been called into question.
19. In the Raynor *et al.* paper, receptor binding studies were performed showing that the kappa receptor could be desensitized (see Figure 1). This is a basis for the conclusion of the paper. There are no charges of misconduct related to that work. There is no evidence that the conclusion that the cloned kappa receptors expressed in COS cells become desensitized are inaccurate. These conclusions have been confirmed, and none of the disputed sample size information nor data is found in the specification.
20. The finding that cloned kappa receptors can be desensitized (based on both receptor binding data and cAMP) have been confirmed in other studies. These studies are reported in a paper by Blake *et al.* ("Blake"; *J. Neurochem.* (1997) 68:1846-1852) which reports that the cloned human kappa receptor expressed in HEK 293 cells can become desensitized. A copy of the Blake paper is attached as Exhibit D. The results and conclusions of the Raynor paper have also been reproduced by another group, and are presented in a paper by Dawson *et al.* ("Dawson"; *J. Neurochem.* (1997) 68:2363-2370). A copy of the Dawson paper is attached as Exhibit E. Thus, the conclusion in the application that the kappa receptor can become desensitized has been confirmed.
21. The results and conclusions of the Raynor paper that the kappa receptor can become desensitized have also been reproduced in my laboratory, and are presented in a manuscript by Tallent *et al.* ("Tallent") that has been submitted for publication, which shows that the mouse

kappa receptor expressed in AtT-20 cells desensitizes. A copy of the Tallent manuscript is attached as Exhibit F.

The Livingston Manuscripts

22. At page 154, line 1 through page 164, line 3 of the specification, there is discussion of studies performed on a delta opioid receptor in which aspartate 128 was mutated to asparagine (D128N). Tables 4, 5, 6 and 7 are included in this section of the specification. These results were included in an initial manuscript that was submitted for publication, with Livingston as the first author ("initial Livingston manuscript"). The Livingston manuscript was never published. The experimental data in the Tables and Figures of the Livingston manuscript are not in dispute. The sample size in the legends of the Figures is in dispute. A copy of the initial Livingston manuscript is attached as Exhibit G.
23. After the initial version of the Livingston manuscript was submitted, a revised version of the Livingston manuscript was submitted ("revised Livingston manuscript"). The data in the revised Livingston manuscript was updated to include the results of additional experiments that had been performed since the submission of the initial Livingston manuscript. The conclusions of the revised Livingston manuscript are the same as the conclusions of the initial Livingston manuscript. A copy of the revised Livingston manuscript is attached as Exhibit H.
24. Tables 1-4 of the initial Livingston manuscript correspond to Tables 4-7 of the specification. The legends of Tables 1-4 of the initial Livingston manuscript and Tables 4-7 of the specification indicate that the results in these Tables represent a compilation of data from three experiments. While in fact three experiments were performed, Livingston, who calculated the results for these Tables, only included the results of one experiment in these Tables.

Therefore, the sample sizes indicated in the legends to these Tables are incorrect. The legends should indicate that the data reported in these Tables are from only one experiment. Since the results from only one experiment were included in these Tables, the included SEM values are meaningless, as SEM values can not be calculated from a single experiment. However, the actual raw data reported in Tables 4-7 are correct for the single experiment reported.

25. The conclusions of the Livingston studies on the D128N mutant are not in dispute. The results of all of the experiments performed by Livingston before and after the patent application was filed were similar to those reported in the specification. Furthermore, the findings of the Livingston studies have recently been reproduced by another group, and are presented in a paper by Befort *et al.* ("Befort"; *Mol. Pharmacol.* (1996) 49:216-223). Befort expressed the D128N mutant in COS cells, as did Livingston, and drew a similar conclusion as that described in the specification. A copy of the Befort paper is attached as Exhibit I.

26. The results and conclusions of the Livingston studies on the D128N mutant described in the specification have also been reproduced in my laboratory, and are presented in a paper by Bot *et al.* ("Bot"; *Mol. Pharmacol.* (1997) 52:272-281), who expressed the D128N mutant in HEK 293 cells. A copy of the Bot paper is attached as Exhibit J.

Reference to an Additional Publication by Kong *et al.*

27. At page 190, there is a reference to Kong *et al.*, *Society of Neuroscience Abstract*. I do not know what results this abstract refers to. No data was included in the abstract or in the specification pertaining to this abstract.

Example X

28. Example X, page 165, line 26 through page 171, line 26 contains a discussion of experiments on chimeric opiate receptors. No data was included in the specification. The results of these experiments were never published, and the conclusions contained in Example X have not been called into controversy.
29. The conclusions described in Example X have been reproduced by another group, and are presented in a paper by Xue and Liu-Chen ("Xue and Liu-Chen"; *J. Biol. Chem.* (1994) 269:30195-30199). A copy of the Xue and Liu-Chen paper is attached as Exhibit K.
30. I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

9/11/97

Date



Terry Reisine